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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,594	11/28/2005	Marc Blondel	0070663-000002	1460

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EXAMINER	
HANLEY, SUSAN MARIE	
ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
07/16/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/531,594	BLONDEL ET AL.	
	Examiner	Art Unit	
	SUSAN HANLEY	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *1-8,15 and 18-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/12/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-8 and 11-21 are pending

Election/Restrictions

Newly submitted claims 18-21 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: They are directed to a different statutory category of invention compared to the elected group. The elected invention is directed to a composition while the new added claims are directed to a method of use. The special technical feature of claims 16 and 17 is that they are drawn to compounds that have particular physical and chemical properties. The special technical feature of claims 18-21 is the step of administering a therapeutically effective dose of the compounds of claims 16 and 17 to a patient that can have a neurodegenerative disease. The two groups lack a special technical feature because the compounds lack a step of administration. They are just compounds with chemical and physical properties.

Claims 16 and 17 are still under examination and not found to be allowable. Hence, there is no rejoinder at this time.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 18-21 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1-8, 11-15 and 18-21 stand withdrawn.

Claims 16 and 17 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16 and 17 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Applicants argue that the *in vitro* tests of the present invention (yeast-based assay) correlate with the claimed method (it is noted that only the composition is under examination); and the model is recognized within the art as correlating to the specified condition. Applicants allege that the disclosed tests are acknowledged as showing anti-prion activity, and thus should be accepted as correlating unless the examiner has evidence to the contrary. Applicants assert that no such evidence has been presented.

Applicants assert that the tests and supporting data of the instant specification are sufficient and reliable indicators of a biological activity of such compounds, and are reasonably predictive that such compounds would be useful for treating prion-associated pathologies.

Applicants have submitted Tribouillard-Tanvier et al. ((2008) PLoS ONE 3(5): e2174; submitted in the IDS filed 11/12/08) to support applicants' assertion of anti-prion activity. The reference allegedly shows the anti-prion effect of the compound 6-aminophenanthridine (6AP) in cell-based assays and *in vivo* in a mouse model for prion-

based disease. *Id.* at pg. 2, left column (data not shown). The 6AP compound was identified by the test model of the instant application.

Applicants further argue that the test model of the instant application also enabled identification of other compounds having *in vivo* anti-prion effect, such as Guanabenz. Applicants allege that Trouillard-Tanvier et al. ((2008) PLoS ONE: 3(4): e1981; cited in the IDS filed 11/12/08) demonstrate the efficacy of Guanabenz against a mammalian prion *(ex vivo* data), and against a murine prion *(in vivo* data). Applicants conclude that this shows that the test model disclosed and used by applicants is a sound model and a reliable indicator of an *in vivo* anti-prion effect.

Applicants' assert that the determination of a therapeutically effective amount of the claimed compounds is something well within the skill set of the ordinary worker in the art. Having been directed to anti-prion compounds and formulations by the instant specification, it would be a matter of routine experimentation for the ordinary skilled worker to determine a therapeutically effective amount. Applicants additionally assert that the instant specification provides ample guidance as to which prion-related diseases may be treated by the claimed pharmaceutical formulation and that such guidance is found, for example, at p. 4, left column (¶ 0059).

Responding to Applicants' arguments that yeast-based assays of the invention correlate with the claimed pharmaceutical composition and that the model is recognized within the art as correlating to the specified condition, there are two situations to consider. Firstly, do the findings using a prion in vivo mouse model correlate with the

same treatment in humans? Secondly, do in vitro studies or the instant yeast-based assay correlate with prion mouse models or with humans suffering from prion diseases? Geschwind (2008) discloses that the only known treatment in humans suffering from a prion disease that has had some success is the administration of quinacrine (p. 531, first full paragraph). However, several studies with mouse models resulted in no benefit in survival for said prion-infected mice. For example, Barret (2003) tested quinacrine by in vitro models as well as a murine model. C57BL6 mice were injected with 6PBI mouse-adapted BSE strain or a control. Mice were administered quinacrine based on a dose comparable to humans (300 mg/day). No curative effect of quinacrine was observed in the mice and there was a slightly increased PrPres signal in the spleen of the infected and treated animals (p.8467 (right col. 2nd full paragraph). Several in vitro studies were also performed on various cell lines and brain homogenates to asses the in vitro effect of quinacrine. The results were mixed, for example, quinacrine efficiently hampered de novo generation of fibrollogneic prion protein and PrPres accumulation in ScN2a cells. However, it was unable to affect the protease resistance of preexisting PrP fibrils and PrPres from brain homogenate. A "curing" effect was observed in ScGT1 cells only after lengthy treatment.

In a review of rodent models for human prion disease, Groschup (2008) teaches that transgenic mouse models have been used to investigate various aspects of prion disease and have advanced the understanding of prion diseases (see abstract). However, Groschup states that most factors which modulate the pathogenesis of prion infection in vivo are still an enigma (page 9/13) , 1st full paragraph). Groschup notes the

difference in prion pathogenesis in various species (p. 9/13 right column). Groschup concludes that "While transgenic mice (independent of whether they were generated by homologous recombination or by microinjection), bank vole, or hamster models are not bona fide models for the prion pathogenesis in humans and animals, they can allow to make better exposure and transmission risk assessment for animals and humans" (page 10/13). Thus, mouse prion models are not a reliable model for human pathogenesis of prion diseases.

Zou (2004) makes similar observation regarding the usefulness of in vitro and in vivo models of human prion diseases and notes that "Although the animal models appear potentially helpful in further characterizing phenotypes of human prion diseases upon passage to animals, great caution must be exercised before equating the disease phenotype produced in an animal model with that of the modeled human disease" (p. 162, penultimate paragraph).

Thus, one can conclude that in vitro results do not predictably correlate with in vivo models or in humans suffering from a prion disease. In vivo studies with "accepted" mouse models do not correlate with human results. Hence, there is a very high degree of unpredictability regarding correlation between or among the various in vitro and in vivo mouse models and human experience with quinacrine which is known to pass through the human blood-brain barrier (Geschwind (2008) page 531, first sentence of first full paragraph).

Regarding the instant case, the disclosed yeast-based assay may correlate with the vivo model disclosed by Tribouillard-Tanvier et al. (2008) references but there is no

evidence that said in vivo mouse model positively correlates with the human experience of prion-based diseases. Furthermore, 6AP is not among the genus of claimed halo-aminophenanthridine compounds of the claimed invention.

Thus, four recent references demonstrate the unpredictability of the correlation of efficacy of treatment among in vitro, in vivo mouse models and the experience of humans suffering from prion disease.

Furthermore, it is noted that the instant specification casts doubt regarding the relevance between yeast prion and mammalian prions. The specification teaches that Prof. Cullin (no complete reference provided) notes that prions (mammal) and propagons (yeast) differ in their location relative to cellular structure, the pathological character of mammal prion as well as some biophysical difference between mammalian and yeast prion (e.g., ternary and quaternary structure; specification page 5, lines 6-19). Hence, it is unclear from the specification if the efficacy of compounds in the disclosed yeast-based prion model actually correlates with human prion diseases.

Thus, taken as a whole, the prior art demonstrates the inconsistency of correlation in efficacy of a treatment among in vitro models and mouse models and in humans having a prion diseases. The instant specification discloses that the claimed compounds exhibit some an vitro anti-prion activity. However, the instant specification casts doubt on the relevance between yeast prion and those that infect human prions There is no disclosure that demonstrates that the disclosed yeast-based assay shows a correlation of treatment outcome with an accepted mouse model (which the prior art demonstrates that there is no such mouse model) compared to that of humans having a

prion diseases at the time the invention was made. The Tribouillard-Tanvier et al. (2008) references (published after the filing date of the instant application) fail to demonstrate a correspondence in efficacy of Guanabenz or 6AP between a mouse model and humans having a prion disease. The Tribouillard-Tanvier et al.(2008) references fail to teach any direct correlation between the results of the disclosed yeast-based assay with the mouse model taught by the reference regarding the compounds of claims 16 and 17. Therefore, there is a very high degree of uncertainty and unpredictability among the results of in vitro, prion mouse models and the instant yeast-based assay compared to human efficacy. The specification does not bridge this gap and Applicant's argument regarding the enablement on this point are non-persuasive.

Responding to Applicants' argument that one of ordinary skill in the art could determine a therapeutically effective dose of the claimed compounds to treat prion diseases in humans, it is unclear to what formulations to which Applicant refers. There are no formulations in the specification that correspond to administration for human treatment. It is unclear how the skilled artisan, much less the ordinary artisan, could determine a therapeutically effective dose using routine experimentation of the compounds of claim 16 and 17 when no such information is provided.

Responding to Applicants' arguments that the instant specification provides ample guidance as to which prion-related diseases may be treated by the claimed pharmaceutical formulation and that such guidance is found, for example, at p. 4, left column (¶ 0059), Paragraph 0059 is not found on page 4, but rather page 3, at the right

column and it does not name prion-related diseases may be treated. It shows the structure of the compound of claim 16.

In conclusion, claims drawn to pharmaceutically acceptable compositions generally require supporting evidence or predictable mechanism of action support because of the unpredictability in biological responses to therapeutic treatments. In particular, prion-related diseases are not well understood and there is no treatment for them except for quinacrine. The specification is directed to screening assays. The correlation among in vitro, yeast-based assays and in vivo mouse models with human efficacy for treatment of prion disease is highly unpredictable. The specification fails to provide guidance that would enable a person of skill in the art to determine which prion-related maladies could be treated by a pharmaceutical composition of the elected compounds. The specification fails to provide guidance at to how the skilled artisan would determine a therapeutically effective amount. Therefore, claims 16 and 17 are not enabled by the disclosure.

Double Patenting

Claim 16 is provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 19 of copending Application No. 11/483,822. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 16 and 17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9, 10 and 17 of copending Application No. 11483822. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 9 and 10 for ‘822 are drawn to a medicament comprising the structure of claim 16 and claims 17. It would be obvious to add a pharmaceutically acceptable vehicle to form a medicament in order to administer a medicament to a subject in need thereof. Claim 17 of ‘822 is drawn to the same genus of compounds as instant claim 17.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUSAN HANLEY whose telephone number is (571)272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sandra Saucier/
Primary Examiner, Art Unit 1651

/Susan Hanley/
Examiner, Art Unit 1651